Kidney Manifestations in Benign Hematological Disorders

By

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Physiologically , there is an intimate link between the *kidney* and the *blood*. Many of the diseases are the result of alteration in the blood such as *dysproteinemia, microangiopathic hemolytic anemia, hemolysis,* etc. on the other hand, the kidney is the organ responsible for regulation of hemostasis.

Renal dysfunction can lead to both anemia and polycythemia. In addition, recent understanding of MAHA process reveals that the renal microvasculature plays a key role in the pathogenesis.

Finally , the failure of the kidney to clear toxins from the body can result in alteration involving hemostasis, as well as leukocyte function and survival.

Intravascular hemolysis

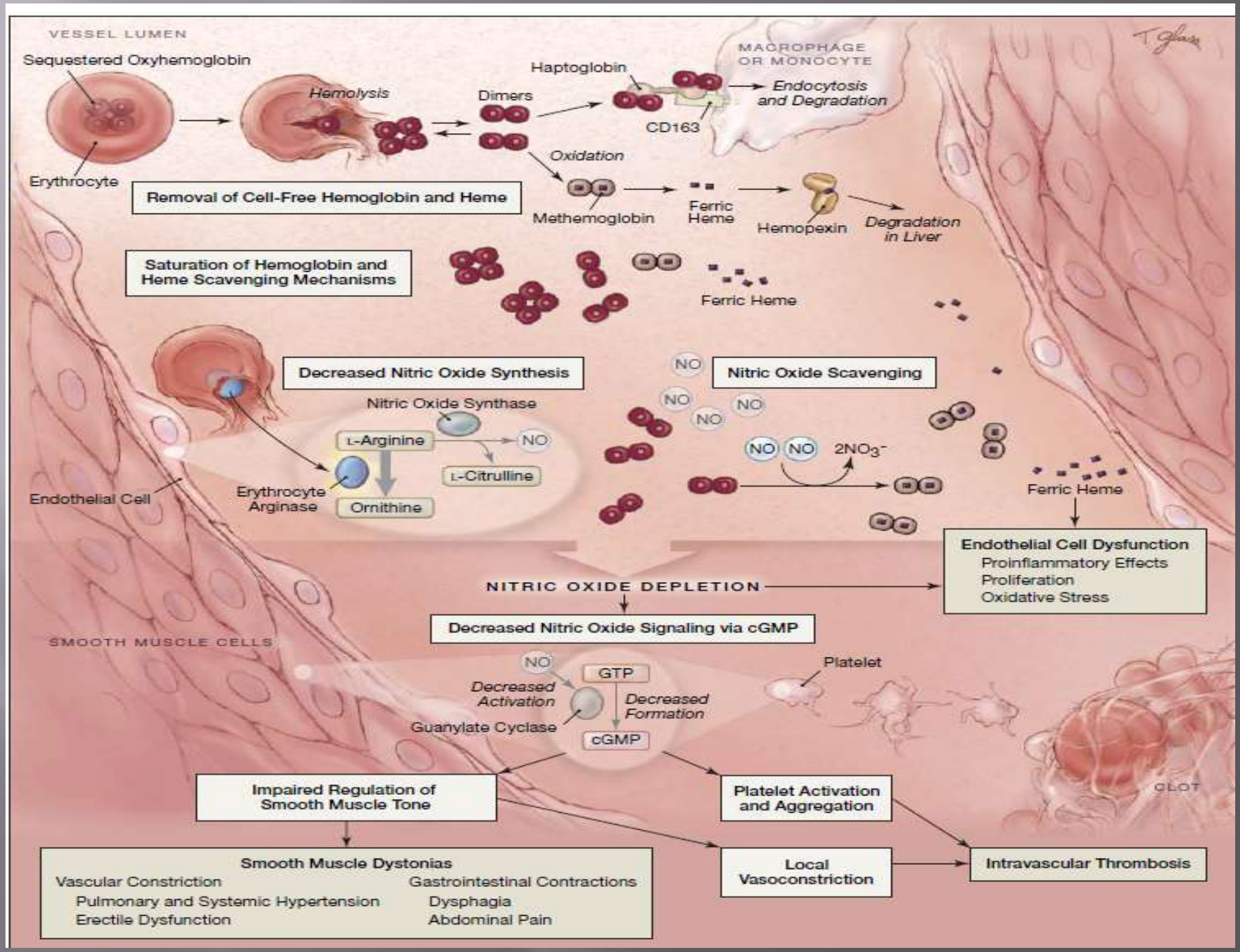
Hemolysis is the destruction or removal of red blood cells from the circulation before their normal life span of 120 days. While hemolysis can be a lifelong asymptomatic condition, it most often presents as anemia when erythrocytosis cannot match the pace of red cell destruction.

The diagnosis is established by *reticulocytosis, increased unconjugated bilirubin* and *lactate dehydrogenase, decreased haptoglobin,* and *peripheral blood smear findings.*

There are two mechanisms of hemolysis. ***Intravascular hemolysis*** is the destruction of red blood cells in the circulation with the release of cell contents into the plasma.

Mechanical trauma from a damaged endothelium, complement fixation and activation on the cell surface, and infectious agents may cause direct membrane degradation and cell destruction.

The more common ***extravascular hemolysis*** is the removal and destruction of red blood cells with membrane alterations by the macrophages of the spleen and liver.


VESSEL LUMEN
Sequestered Oxyhemoglobin
Erythrocyte
Hemolysis
Dimers
Haptoglobin
CD163
MACROPHAGE OR MONOCYTE
Endocytosis and Degradation
Oxidation
Methemoglobin
Ferric Heme
Hemopexin
Degradation in Liver
Removal of Cell-Free Hemoglobin and Heme
Saturation of Hemoglobin and Heme Scavenging Mechanisms
Ferric Heme
Decreased Nitric Oxide Synthesis
Nitric Oxide Synthase
L-Arginine
NO
L-Citrulline
Ornithine
Erythrocyte Arginase
Endothelial Cell
Nitric Oxide Scavenging
NO
NO NO
2NO3-
Ferric Heme
Endothelial Cell Dysfunction
Proinflammatory Effects
Proliferation
Oxidative Stress
NITRIC OXIDE DEPLETION
Decreased Nitric Oxide Signaling via cGMP
SMOOTH MUSCLE CELLS
NO
GTP
Decreased Activation
Decreased Formation
Guanylate Cyclase
cGMP
Platelet
Impaired Regulation of Smooth Muscle Tone
Platelet Activation and Aggregation
Local Vasoconstriction
Intravascular Thrombosis
CLOT
Smooth Muscle Dystonias
Vascular Constriction
Pulmonary and Systemic Hypertension
Erectile Dysfunction
Gastrointestinal Contractions
Dysphagia
Abdominal Pain

Hemoglobinuria and Renal Dysfunction.

Hemoglobinuria is one of the most prominent clinical signs of excessive intravascular hemolysis. Plasma hemoglobin is normally filtered through the glomerulus and actively reabsorbed in proximal tubule cells where it is catabolized with release of iron in the form of hemosiderin.

When the kidney's reabsorption capacity is exceeded, clinically significant hemoglobinuria occurs. Acute renal failure may occur during severe episodes of hemoglobinuria.

Persistent severe hemoglobinuria is also associated with substantial proximal tubule hemosiderin deposition, Fanconi syndrome (defective renal reabsorption of small molecules leading to hyperaminoaciduria, glycosuria, hyperphosphaturia, and bicarbonate and water loss), and chronic renal failure.

Hemolytic conditions with substantial intravascular hemolysis include *paroxysmal nocturnal hemoglobinuria (PNH), sickle-cell disease (SCD), thalassemias, hereditary spherocytosis* and *stomatocytosis, microangiopathic hemolytic anemias, pyruvate kinase deficiency, ABO mismatch transfusion reaction.*

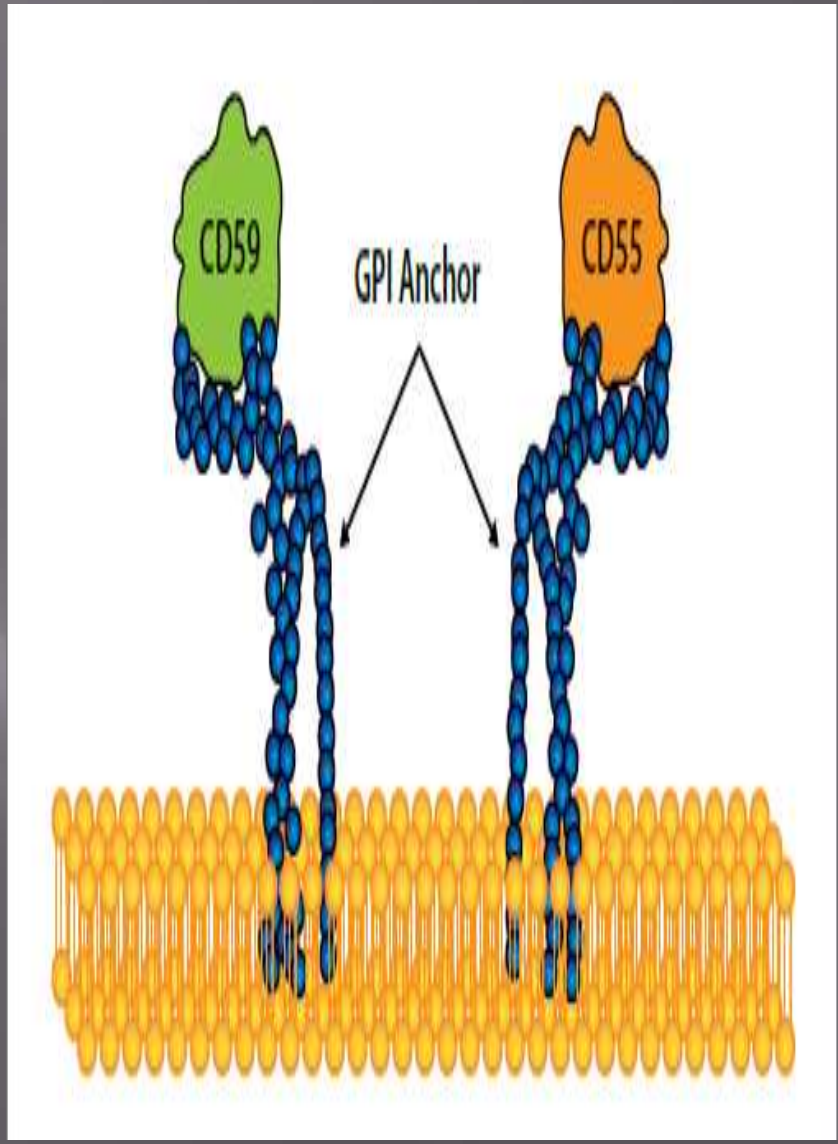
Paroxysmal Nocturnal Hemoglobinuria:

PNH is a rare acquired clonal disorder, affecting all the three blood cell lines. It arises from an inactivating somatic mutation in the phosphatidylinositol glycan class A(PIG-A) gene on x-chromosome necessary for the biosynthesis of a particular glycophosphatidylinositol (GPI) anchor.

This GPI anchor attaches a number of crucial protective proteins to the external membrane surface of blood cells. Its absence results in absence of theses proteins.

Two of these are complement defense proteins *CD55* (PNH decay accelerating factor-DAF) and *CD59* which block complement activation on the cell surface.

Deficiency of the GPI-anchored complement regulatory proteins CD55 and CD59 accounts for intravascular hemolysis which is primary clinical manifestation of the disease. The two other common manifestations of PNH are venous thrombosis and bone marrow failure.



Hemoglobinuria is intermittent in most patients and hemosiderinuria is usually present. Since hemolysis is due to abnormal sensitivity of the RBCS to the lytic action of the complement, it manifests when complement cascade is activated, most aften by infection. The hemolysis is aften paroxysmal, but contrary to the name, need not to be strictly nocturnal.

Hemoglobinuria subsequent to intravascular hemolysis underlies the occurance of acute renal failure in PNH.

Hemoglobin induced acute tubular necrosis (ATN) is most commonly after blood transfusion reactions. The mechanisms underlying the impairment of GFR in intravascular hemolysis include *intrarenal vasoconstriction*, *intratubular obstruction* and *tubular toxicity*.

The product of hemolysis have been found to induce intrarenal vasoconstriction, probably by scavenging the vasodilator nitric oxide (NO) in the renal microcirculation.

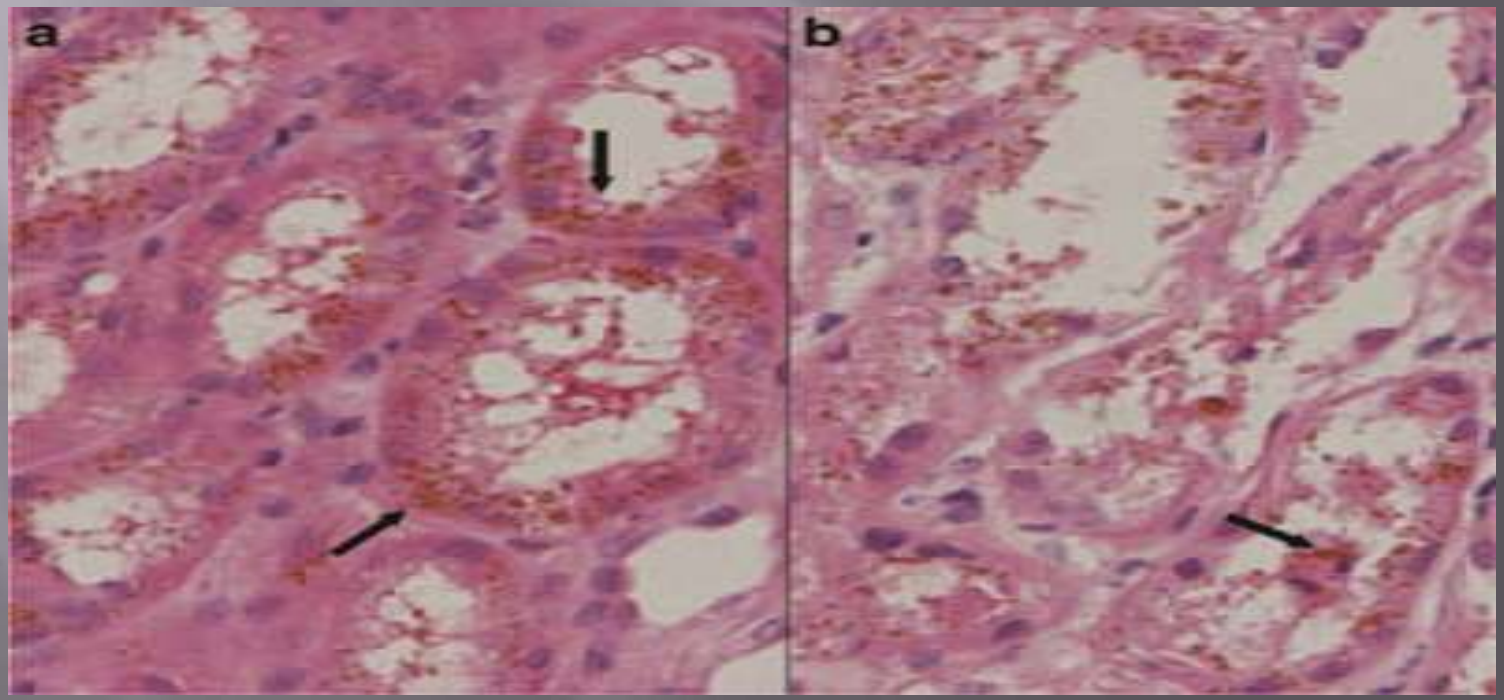
At acidic PH, hemoglobin is also a source of ferrihemate, a substance that is potent inhibitor of tubular transport. Hypovolemia and acidosis have been found to predispose to pigment induced ATN.

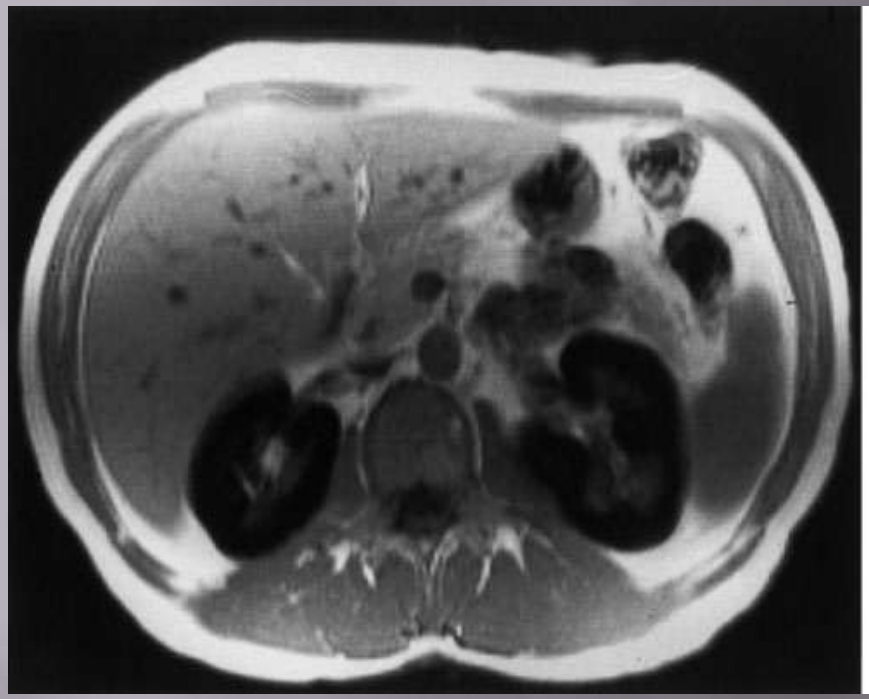
Hemoglobin may also potentially induce tubular injury by stimulating local production of OH^-. The combination of *renal ischemia* along with *ferrihemate* deposition produces acute tubular dysfunction and cell injury.

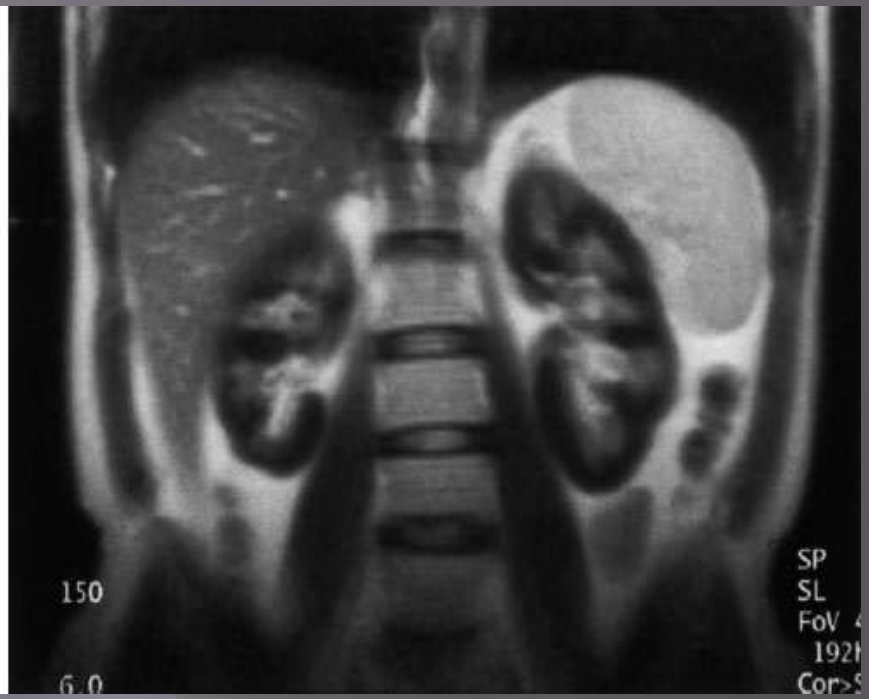
Hemoglobin filtered from the glomerular during an episode of hemoglobinuria is converted to methemoglobin in the acidic milieu of the distal tubule, which leads to its precipitation.

The occlusion of the distal tubule by the precipitates cause stasis of the urine allow greater time for endocytosis of hemoglobin from the proximal tubule, and the iron released from this dissociation cause free radicle oxidant injury.

On histological examination, hemosiderin deposition in the proximal tubules was a common feature in most patients, irrespective of renal function. Renal microinfarcts and interstitial fibrosis has been proposed as a cause of gradual decline of renal function.



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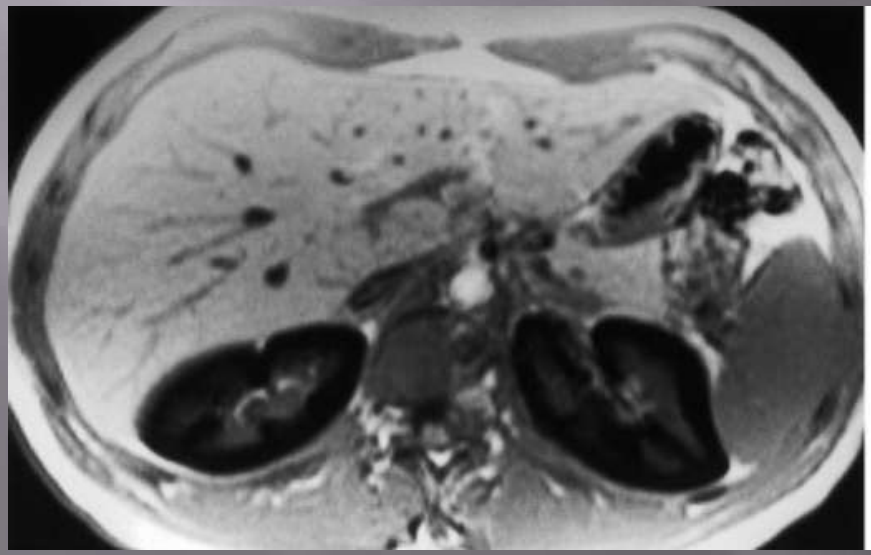
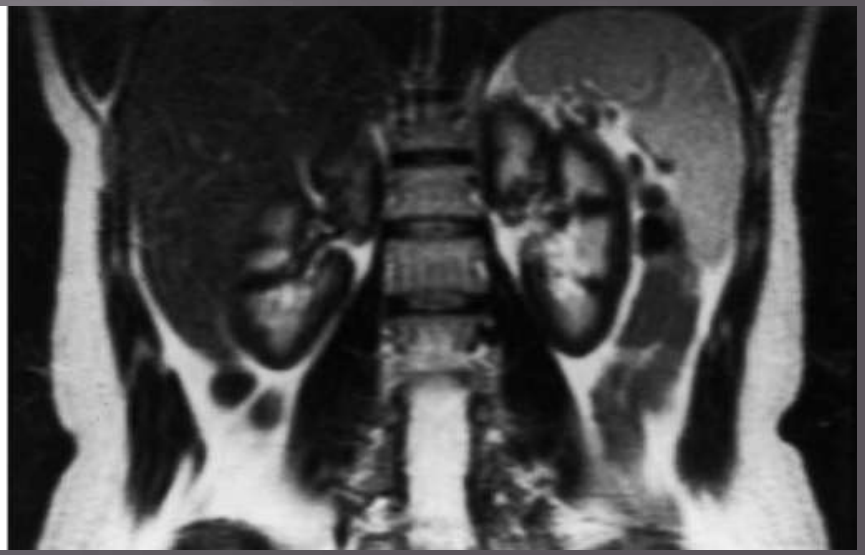




Treatment

-Transfusion therapy

-Corticosteroids may have a role in attenuating acute hemolytic exacerbation.

-A huminised monoclonal antibody against complement C5 (eculizumab).

-Treatment of Thrombosis .

-Stem cell transplantation.

Sickle cell disease (SCD)

Hemoglobin S (HbS) is the most common and well-known structural hemoglobinopathy in the world. This abnormality causes sickle cell disease (SCD), which is a group of disorders that includes the most severe homozygote state (HbSS) and the double heterozygote states (HbSC and HbS, thalassemia).

In this condition a point mutation occurs in the gene encoding the beta chain of hemoglobin (chromosome 11), which causes the amino acid *valine* to replace *glutamic acid* in the sixth position.

This change make the molecule of hemoglobin less soluble and precipitates the formation of polymers under certain conditions (acidosis, hypoxia, and dehydration).

The sickle cells, deformed and rigid, adhere to the vascular endothelium and obstruct small postcapillary venules, leading to occlusion and infarction. After some time, the change in the shape of the erythrocyte is irreversible because of damage to the cell membrane, shortening its half-life and causing hemolysis.

When hemolysis occurs, lactate dehydrogenase, potassium, hemoglobin, oxygen free radicals, and arginase are released into peripheral blood. This phenomenon leads to self-activation and deterioration of endothelial function that in turn promotes a procoagulant state and recruitment of leukocytes.

This helps to spread the chronic vascular inflammatory component of the syndrome and to cause heterocellular aggregate formation between activated leukocytes and sickle cells, contributing to the vaso-occlusive phenomenon.

Pathophysiology of Renal Manifestations

In SCD, under physiological conditions, oxygen pressure in the renal medulla is equal to or less than 20 mmHg . From *childhood*, the hyperosmolarity, low oxygen concentrations, and acidosis in the renal medulla cause the polymerization of hemoglobin, which starts at tensions below 45 mmHg.

Erythrocytes "dehydrated" by these conditions have a high concentration of HbS, which precipitates. Initially, blood viscosity increases locally, the venous capillaries are filled with sickle cells, and interstitial edema occurs. Sickle cell obstruction of the vasa recta causes microthrombosis, infarction, and collateral vessel formation.

This leads to a reduction in the number of functioning vasa recta and loss of normal architecture of the renal medulla, which interferes with the countercurrent mechanism necessary for urine concentration and water-electrolyte balance.

In *late childhood and adolescence*, the permeability of capillaries increases and erythrocytes enter the collecting system with a complete loss of the vasa recta. Blood flow in the renal cortex and the glomerular filtration rate (GFR) increase owing to the secretion of prostaglandins, which causes vasodilatation in the renal medulla. This increased flow in the renal cortex leads to glomerular hypertrophy (glomerulomegaly).

In *adulthood,* when glomerular damage is established, the GFR begins to decline during the third and fourth decades until end-stage renal disease (ESRD) is reached. The continuous transfusions required by these patients can cause renal tubular siderosis

Sickle cell nephropathy

Patients with SCD may develop proteinuria and renal failure that progresses into terminal chronic kidney disease (CKD). The renal involvement responsible is a glomerulopathy whose initial marker is albuminuria.

The prevalence increases with age, ranging between 21.3% and 28% in patients aged 3 to 20 years, of which 10.5% of cases progress to proteinuria within a 20-month follow-up period. In most cases (72%) it continues to progress into renal failure.

the survival time after diagnosis of ESRD is 4 years despite treatment with dialysis. Median survival is approximately 29 and 51 years with and without renal failure, respectively.

When albuminuria appears in SCD patients, the glomerular ultrafiltration coefficient is significantly reduced compared to SCD patients without albuminuria, even in those with preserved GFR, meaning that albuminuria is a very sensitive marker for the glomerular damage caused in SCD.

Proteinuria is associated with higher levels of anaemia, haemolysis, and reticulocytosis, and has also been correlated with the incidence of painful crises, cholelithiasis, acute chest syndrome, and stroke.

Four different types of glomerulopathy have been described in SCD: *idiopathic focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), glomerulopathy specific to SCD,* and *thrombotic microangiopathy (TMA*).

The most common glomerulopathy is FSGS, there are different subtypes: *NOS*, *tip*, *perihilar*, and *collapsing*, as well as *mixed* forms.

Interstitial fibrosis is frequently observed with tubular atrophy adjacent to sclerotic glomeruli. Since this disease mainly affects juxtamedullary glomeruli vascularised by the vasa recta, it is frequently accompanied by severe medullary fibrosis. Both immunofluorescence and electron microscope analyses provide evidence of an absence of immune deposits.

Treatment

-Renin-angiotensin-aldosterone system inhibitors.

-Blood transfusion

-Hydroxyurea

Hematuria and renal papillary necrosis

Hematuria:

This is the most common form of SCD. It can be microscopic, or more commonly, macroscopic and self-limiting. It is frequently unilateral, and is more often found in the left kidney, due to the longer left renal vein and its anatomical location, compressed between the aorta and the superior mesenteric artery.

This subjects this vessel to a greater venous pressure with relative hypoxia in the renal medulla that favours cell sickling.

Haematuria is probably a consequence of cell sickling in the renal medulla combined with vascular obstruction and extravasation of erythrocytes.

The medullary environment is by nature prone to producing sickle cells due to the low pressure of O2, below the sickling threshold of 45mm Hg, along with high osmolarity that dehydrates erythrocytes and concentrates the HbS and the acidic pH that also increases the probability of sickling.

Although hematuria is common in patients with SCD, other causes of hematuria should be excluded.

Treatment

-Given the fact that the hematuria is generally self-limited, treatment is conservative.

- Bed rest, oral hydration, and control of the hematocrit are needed in most cases.

-DDAVP .

-Epsilon-aminocaproic acid (EACA)

-Hydroxyurea.

-Antioxidants.

Renal papillary necrosis

The renal medulla and papilla are particularly vulnerable to ischemic necrosis owing to their hypertonic environment and the peculiar arrangement of their blood perfusion. Even in the healthy adult, there is a state of hypoxia owing to the low blood flow of the vasa recta. Thus, all conditions that reduce blood flow may cause ischemic necrosis of the medulla.

The clinical presentation is very variable: RPN may appear as *macroscopic hematuria* with or without *renal colic* or as *acute urinary retention* secondary to obstruction of detached papillae. It may also present as a *urinary tract infection* or *sepsis*.

Urinalysis may show detached papillae . Traditionally, excretory urography was the key to diagnosis, and today this is true of renal and bladder ultrasound and computed tomography (CT).

The earliest finding in RPN is increased echogenicity in the medullary pyramids (the innermost region of the medulla), which, in the absence of hypercalciuria in a patient with SCD and haematuria suggests RPN.

In later stages, calcification may appear in the medullary pyramids with a typical ‘garland pattern’ surrounding the renal pelvis, or a defect in echogenicity in the pyramids due to detachment of the papilla.

Treatment

1-Aggressive antibiotic therapy .

2-Manual bladder washing .

3-avoid use of anti-inflammatory drugs.

Urinary tract infections

Patients with SCD have reduced humoral immune response due to splenic infarctions, which predisposes them to encapsulated bacterial infections, including urinary tract infections (UTI).

An increased incidence of pyelonephritis has been identified during pregnancy in patients with SCD. Pregnant women with SCD have an increased risk of pyelonephritis and a higher risk of asymptomatic bacteriuria .

As in other infections, UTI can cause sickle cell crises, which should be taken into consideration in children due to the higher frequency of asymptomatic UTI.

Renal medullary Carcinoma

Renal medullary cancer (RMC) is a very rare tumor that appears at a relatively young age, is very aggressive, and is almost exclusively related to the sickle cell trait.

Prognosis is very poor despite surgical treatment and chemotherapy. RMC represents about 2% of all primary renal tumors from 10 to 20 years of age.

Its etiology is unknown, although recent genetic analysis seems to yield similarities between this tumor and the renal pelvis urothelium.

The most common symptoms at diagnosis are *flank or abdominal pain, macroscopic hematuria* with or without clots, and *systemic symptoms related to metastatic disease*.

The tumor is located on the right side in 75% of cases. The diagnosis of RMC must be considered in any young patient with sickle cell trait and hematuria.

Survival after surgery varies from 1 to 5 months. At the time of diagnosis it is not uncommon to find metastases in the lung, liver, mediastinum, or retroperitoneum and lymphatic, venous, or renal cortex invasion.

Recently ,genetic study of the tumor found overexpression of RNA for Topo II alpha, and that makes the tumor is sensitive to chemotherapy with inhibitors of Topo II alpha (actinomycin D, doxorubicin, and etoposide) and may be effective as first-line treatments for RMC.

The macrophage stimulating receptor 1 (c-met-related tyrosine kinase) is also overexpressed, suggesting a possible utility of inhibitors of tyrosine kinase (imatinib, sorafenib, and sunitinib) in this disease.

Thrombotic Microangiopathy (TMA)

TMA, is the pathological process that represents the final common pathway of many disease entities. Clinically, TMA is considered as a family of closed-related syndromes recognized by the development of new onset *thrombocytopenia*, *microangopathic hemolytic anemia* with *schistocytes* in the peripheral blood, and *multiple organ thrombosis*.

The pathological process of TMA begins with an abnormal biochemical triggering or pathological insult, that damage the endothelium via multiple and varied mechanisms. Then, functionally altered endothelium provokes intravascular platelet aggregation or activation of coagulation factors that leads to widespread microvascular thrombosis.

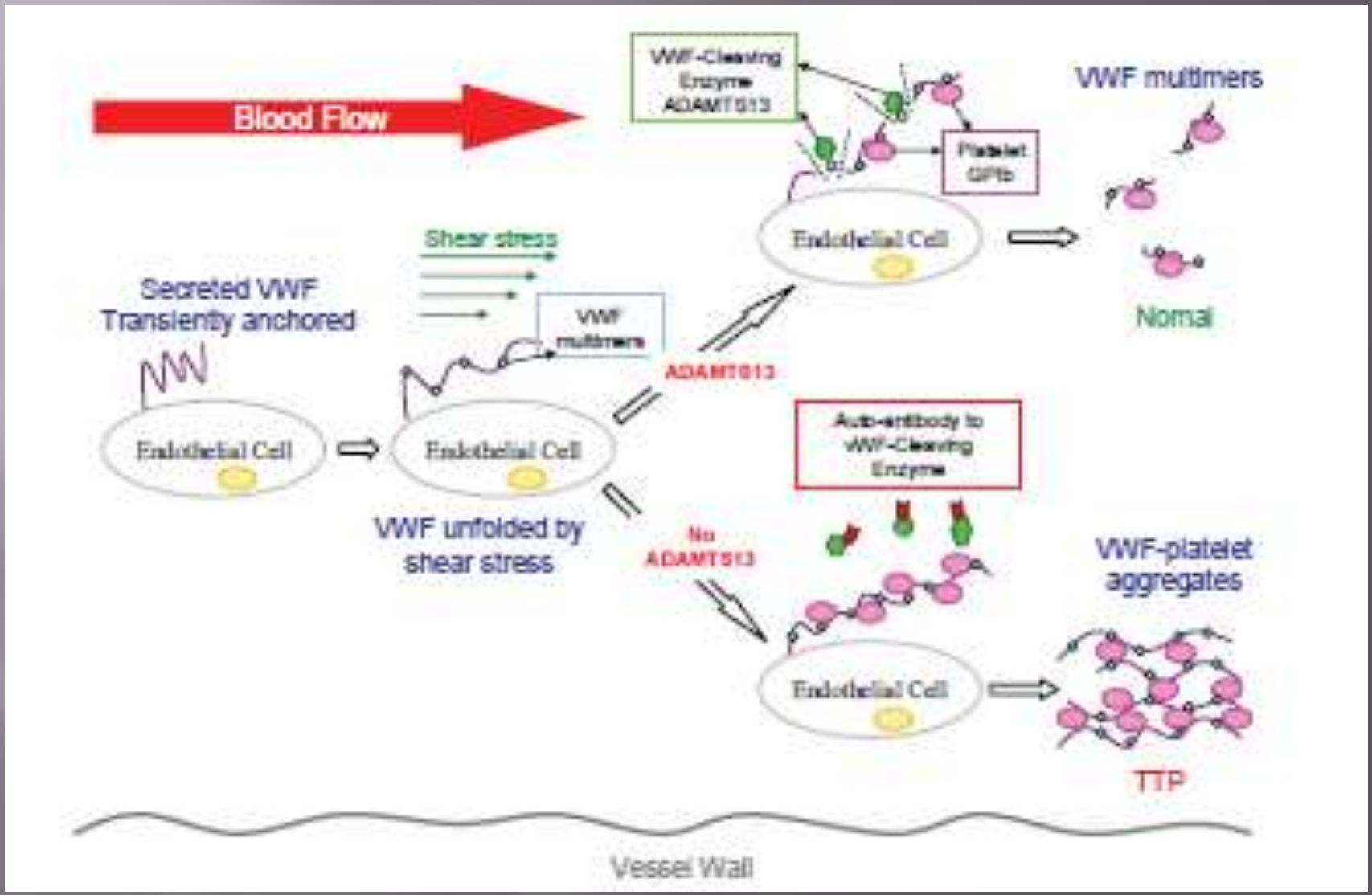
The clinical spectrum of TMA includes a group of disorders, such as: *TTP-HUS, catastrophic antiphospholipid antibody syndrome, systemic vasculitis, malignant hypertension, scleroderma in renal crisis, disseminated malignancy, pre-eclampsia/eclampsia, stem cell transplantation related TMA, cancer and chemotherapy related TMA,* and *DIC*.

Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome

Patients with *TTP* were originally classified by a *pentad* of symptoms including *thrombocytopenia*, *microangiopathic hemolytic anemia*, *fluctuating neurological signs*, *renal impairment*, and *fever*.

HUS is defined as the combination of a *microangiopathic hemolytic anemia* with variable degrees of *thrombocytopenia* and *renal failure*. The syndrome usually occurs in previously healthy children and often is preceded by a gastrointestinal enteritis.

Pathogenesis of idiopathic thrombotic thrombocytopenic purpura



Renal abnormalities

Proteinuria and *hematuria* are common in TTP. In contrast, acute renal failure with marked azotemia, fluid overload, hypertension, and need of dialysis, is much less frequent

The renal manifestations of hematuria, proteinuria, and mild impairment of the clearance function in TTP are consistent with the focal and segmental distribution of microthrombi most commonly observed.

Pathological examination reveals *microthrombi* typically affect one or a few segments of the glomeruli. Although the extent of glomerular thrombi varies widely among the patients, widespread glomerular or cortical necrosis and fibrosis are uncommon in TTP.

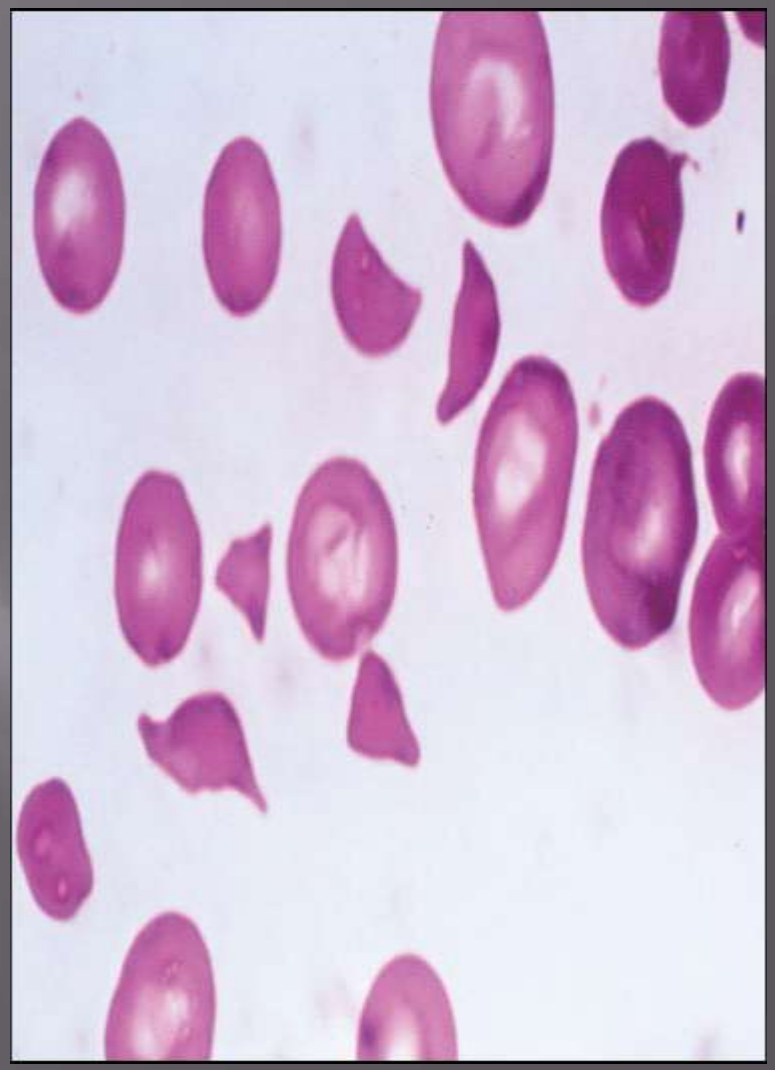
Pathogenesis of Hemolytic uremic syndrome

D+ HUS is associated with an infection with verocytotoxin(VT)- or Shiga-like toxin-producing *E coli* 0157:H7, *Shigella dysenteriae* type 1, *E coli* 026:H11, and other infectious agents. At least three different toxins are designated as VT-1, VT-2, and VT-2c. The toxin binds, invades, and destroys colonic mucosal epithelial cells, resulting in bloody diarrhea.

After entering the systemic circulation, the toxin attaches to a membrane glycosphingolipid receptor (globotriaosylceramide) on endothelial cells (especially in the kidney). The endothelial cells swell and are injured.

In the process, certain endothelial products are released (eg, von Willebrand factor, platelet aggregating factor, plasminogen activator inhibitor-1), and platelet/fibrin thrombi form in these injured areas. In addition to the kidney, the pancreas, brain, and other organs may be injured.

The circulating red blood cells that are forced through these occluded vessels are deformed and fragment, which produces the characteristic schistocytes. These fragmented red cells are removed by the reticuloendothelial system, resulting in hemolytic anemia. Because platelets are consumed in the process of vascular injury, most patients also develop some degree of thrombocytopenia.



Renal Aspects

Renal involvement in HUS can vary from mild to severe. Children in whom the renal involvement is mild have only *microscopic hematuria, minimal proteinuria,* and *normal urine output.*

Some may have an increased urine volume. Severe involvement is characterized by *anuria, widespread renal cortical necrosis,* and *irreversible anuric renal failure.* Most affected children have features between these two extremes.

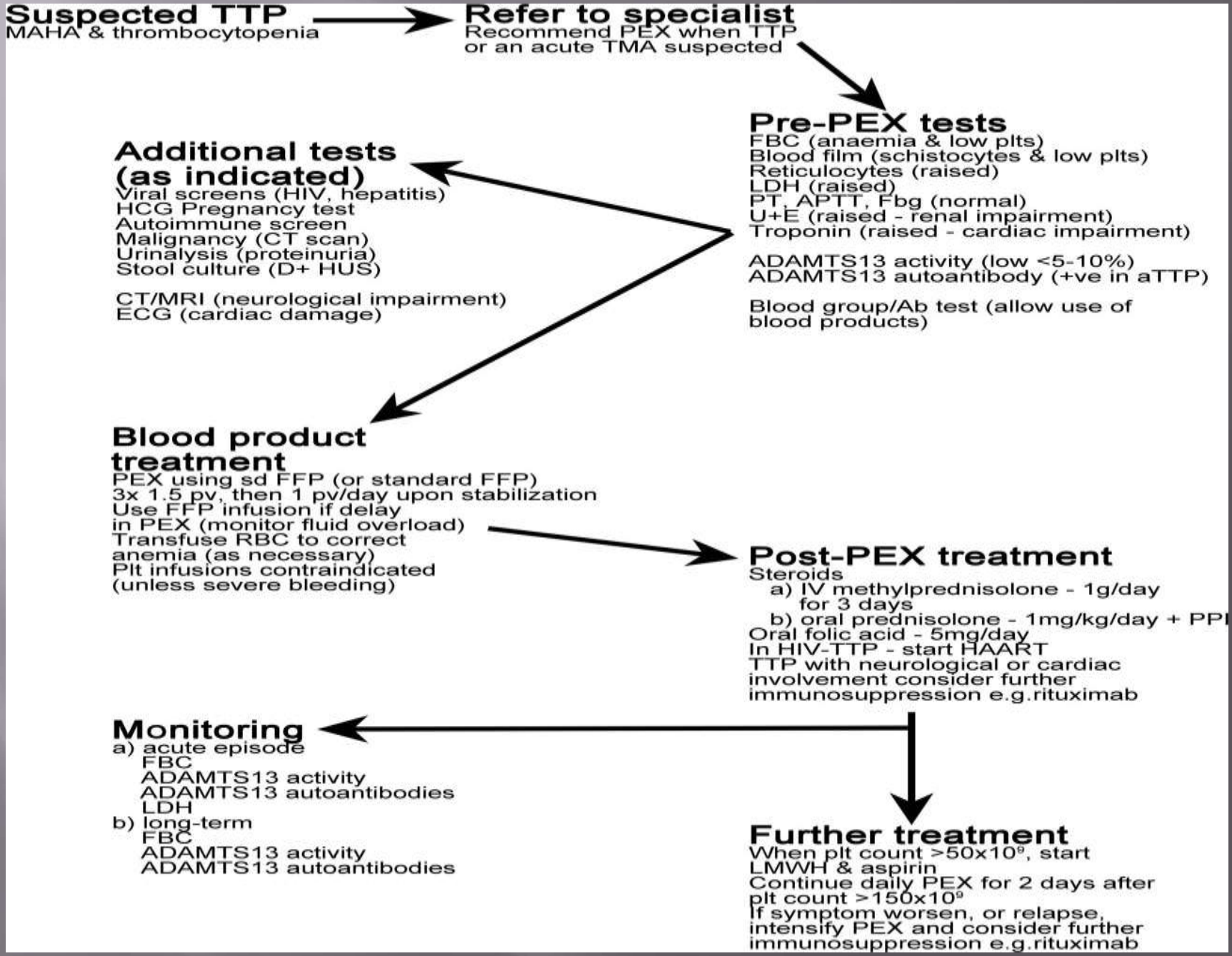
The majority of patients (60%) experience oliguria that lasts an average of 1 week. Almost 50% are anuric for an average of 3 days. If there is oligoanuria, it can continue for weeks. All patients have hematuria and proteinuria unless anuric. Red blood cell casts frequently are found if carefully sought.

Renal dysfunction is indicated by elevated serum levels of creatinine and blood urea nitrogen (BUN). A variety of fluid and electrolyte imbalances occur because of reduced renal function, hemolysis, and tissue catabolism.

These include *hyponatremia* that is usually dilutional; *hyperkalemia* from reduced glomerular filtration rate, hemolysis, and tissue catabolism; *metabolic acidosis* from reduced renal function and tissue catabolism; and *hyperphosphateria* and *hypocalcemia*. *Fluid overload* is common and can lead to edema and cardiac failure.

Hypertension is a common feature of HUS. It occurs at some point in the illness in almost 50% of children and can be severe. The etiology of hypertension often is obscure. Studies have reported both increased and normal renin activity. Volume overload caused by reduced renal function with fluid retention is another potential case of hypertension.

Renal biopsy rarely is needed in children who have the characteristic clinical and laboratory features of HUS. It may be helpful following resolution of the acute phase of the illness to determine the degree of chronic injury and, therefore, long-term prognosis.


Suspected TTP
MAHA & thrombocytopenia
Refer to specialist
Recommend PEX when TTP or an acute TMA suspected
Pre-PEX tests
FBC (anaemia & low plts)
Blood film (schistocytes & low plts)
Reticulocytes (raised)
LDH (raised)
PT, APTT, Fbg (normal)
U+E (raised - renal impairment)
Troponin (raised - cardiac impairment)
ADAMTS13 activity (low <5-10%)
ADAMTS13 autoantibody (+ve in aTTP)
Blood group/Ab test (allow use of blood products)
Additional tests (as indicated)
Viral screens (HIV, hepatitis)
HCG Pregnancy test
Autoimmune screen
Malignancy (CT scan)
Urinalysis (proteinuria)
Stool culture (D+ HUS)
CT/MRI (neurological impairment)
ECG (cardiac damage)
Blood product treatment
PEX using sd FFP (or standard FFP)
3x 1.5 pv, then 1 pv/day upon stabilization
Use FFP infusion if delay in PEX (monitor fluid overload)
Transfuse RBC to correct anemia (as necessary)
Plt infusions contraindicated (unless severe bleeding)
Post-PEX treatment
Steroids
a) IV methylprednisolone - 1g/day for 3 days
b) oral prednisolone - 1mg/kg/day + PPI
Oral folic acid - 5mg/day
In HIV-TTP - start HAART
TTP with neurological or cardiac involvement consider further immunosuppression e.g.rituximab
Monitoring
a) acute episode
FBC
ADAMTS13 activity
ADAMTS13 autoantibodies
LDH
b) long-term
FBC
ADAMTS13 activity
ADAMTS13 autoantibodies
Further treatment
When plt count >50x10⁹, start LMWH & aspirin
Continue daily PEX for 2 days after plt count >150x10⁹
If symptom worsen, or relapse, intensify PEX and consider further immunosuppression e.g.rituximab

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a clinicopathological syndrome which complicates a range of illnesses. It is characterized by systemic activation of pathways leading to and regulating coagulation, which can result in the generation of fibrin clots that may cause organ failure with concomitant consumption of platelets and coagulation factors that may result in clinical bleeding.

Conditions associated with DIC

Infections

Acute DIC: Bacteria and their toxins, fungi, viruses, rickettsiae

Chronic DIC: Chronic infection. e.g., tuberculosis, abscesses, osteomyelitis

Obstetrical complications

Acute DIC: Abruptio placentae, abortions (especially therapeutic and septic abortions), amniotic fluid

embolism, hemorrhagic shock

Chronic DIC: Dead fetus syndrome

Trauma

Acute DIC: Polytrauma; neurotrauma

Venoms

Acute DIC: Snake bites and rarely spider bites

Malignancy

Acute DIC: Acute promyelocytic leukemia, acute

myelomonocytic or monocytic leukemia, disseminated

prostatic carcinoma

Chronic DIC: Gastrointestinal, lung and breast malignancy

Vascular disease

Acute DIC: Brain infarction or hemorrhage

Chronic DIC: Aortic aneurysm, giant hemangioma

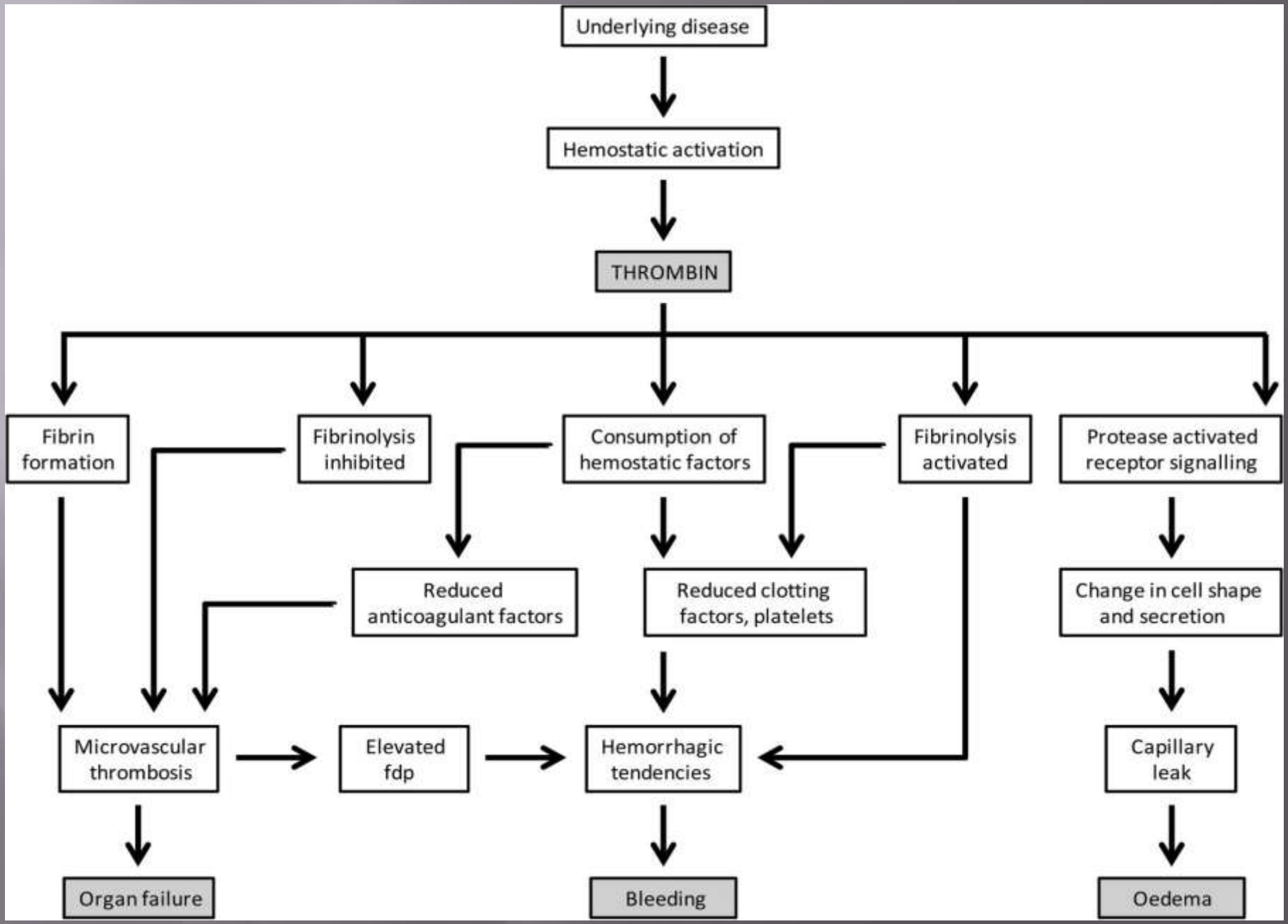
Noninfectious inflammatory diseases

Inflammatory bowel disease: Crohn's disease and similar disorders

Others

Acute DIC: Heparin-induced thrombocytopenia with thrombosis (HITT); purpura fulminans in newborns

(homozygous protein C deficiency); transfusion of ABO incompatible red cells.


Underlying disease
Hemostatic activation
THROMBIN
Fibrin formation
Fibrinolysis inhibited
Consumption of hemostatic factors
Fibrinolysis activated
Protease activated receptor signalling
Reduced anticoagulant factors
Reduced clotting factors, platelets
Change in cell shape and secretion
Microvascular thrombosis
Elevated fdp
Hemorrhagic tendencies
Capillary leak
Organ failure
Bleeding
Oedema

Currently available diagnostic criteria to diagnose DIC

	ISTH criteria	JMHW criteria	JAAM criteria
Underlying clinical condition predisposing to DIC	Essential	1 point	Essential
Clinical symptoms	Not used	Bleeding = 1 point; organ failure = 1 point	SIRS score ≥ 3 = 1 point
Platelet count ($\times 10^9$/L)	50-100 = 1 point < 50 = 2 points	80-120 = 1 point 50-80 = 2 points < 50 = 3 points	80-120 or > 30% reduction = 1 point < 80 or > 50% reduction = 2 points
Fibrin-related marker	Moderate increase = 2 points Marked increase = 3 points	FDP 10-20 μg/mL = 1 point FDP 20-40 μg/mL = 2 points FDP > 40 μg/mL = 3 points	FDP 10-25 μg/mL = 1 point FDP > 25 μg/mL = 3 points
Fibrinogen	< 1 = 1 point	1-1.5 = 1 point < 1 = 2 points	Not used
PT	Prolongation 3-6 sec = 1 point Prolongation > 6 sec = 2 points	PT ratio 1.25-1.67 = 1 point PT ratio > 1.67 = 2 points	PT ratio ≥ 1.2 = 1 point
DIC diagnosis	≥ 5 points	≥ 7 points	≥ 4 points

Acute renal failure

Acute renal failure occurs in 25 to 40 percent of patients with acute DIC. Two major mechanisms are involved:

1-microthrombosis of afferent arterioles may produce cortical ischemia or necrosis, and hypotension and/or sepsis can lead to acute tubular necrosis.

2-Endotoxin-induced endothelial injury may predispose to intrarenal thrombus formation by directly promoting platelet aggregation, by diminishing the release of nitric oxide (endothelium-derived relaxing factor), which normally inhibits platelet aggregation, and by increasing the synthesis of plasminogen activator inhibitor type 1, leading to a reduction in fibrinolytic activity.

Treatment

1-Because DIC develops secondary to other diseases, the cornerstone of therapy *is the treatment of the underlying disorder*. Its prompt recognition is therefore important in improving the outcome.

2-*Transfusion support.*

3-Modulating thrombin generation

-Heparin

-Anticoagulant factor concentrate: AT,APC,TM

4-Modulating profibrinolytic activity

Antiphospholipid syndrome

The Antiphospholipid syndrome (APS) is a prothrombotic condition characterized by venous or arterial thrombosis and/or pregnancy morbidity in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPLs).

aPLs are autoantibodies that target phospholipid-bound proteins, notably β2-glycoprotein I (β2GPI).

The disorder is referred to as primary when it occurs in the absence of another autoimmune disease. Secondary APS occurs in the context of an autoimmune disorder such as systemic lupus erythematosus.

Classification criteria for definite APS

Clinical criteria (1 or more of the following)	Laboratory criteria (1 or more of the following present on 2 or more occasions at least 12 weeks apart using recommended procedures)
Vascular thrombosis: 1 or more objectively confirmed episodes of arterial, venous or small vessel thrombosis occurring in any tissue or organ ***Pregnancy morbidity***: 1 or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or 1 or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, preeclampsia, or placental insufficiency; or 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation	LA detected according to the guidelines of the ISTH ACL antibody of IgG and/or IgM isotype, present in medium or high titer (40 IgG or IgM phospholipid units or the 99th percentile) measured by a standardized ELISA Anti–2GPI antibody of IgG and/or IgM isotype present in titer the 99th percentile measured by a standardized ELISA

- ***Definite APS is present if at least 1 clinical criteria and 1 laboratory criteria are met***

The Catastrophic APS (CAPS) is a rare life-threatening form of APS in which widespread intravascular thrombosis results in multiorgan ischemia and failure. CAPS is the initial presentation of APS in nearly half of patients, while the remaining half has a history of APS.

Putative Pathogenic Mechanisms in CAPS

- **Cellular activation**

Endothelial cell activation
Immune cell activation
Platelet activation

- **Inhibition of anticoagulants**

Inhibition of the protein C pathway
Disruption of annexin A5 shield

- **Inhibition of fibrinolysis**

Inhibition of tissue plasminogen activator (tPA)
Blocking of β^2-glycoprotein I
Blocking of annexin A2

- **Complement activation**

Endothelial cell activation by C5a and MAC
Immune cell activation by C5a
Platelet activation by C3a and MAC
Inhibition of fibrinolysis by C5a

Preliminary criteria for the classification of CAPS

- **Criteria**

1. Evidence of involvement of 3 or more organs, systems and/or tissues
2. Development of manifestations simultaneously or in 1 week
3. Confirmation by histopathology of small vessel occlusion in at least 1 organ or tissue.
4. Laboratory confirmation of the presence of aPL antibodies.

- **Classification criteria**

Definite CAPS

All 4 criteria present

Probable CAPS

- ✓ 1, 2, and 4
- ✓ 1, 3, and 4; however, a third event occurs between a week and a month, despite anticoagulation
- ✓ 1-4; however, only two organs/tissues are involved
- ✓ 1-4; however, antiphospholipid antibodies could not be assayed six weeks apart due to death of a patient who was never tested before

Clinical Manifestations

Approximately 72% of patients with CAPS were women . The age of patients ranged from 11 to 60 years with a mean of 37 years. *A precipitating factor* such as infection (22%), surgery (10%), discontinuation of anticoagulation (8%), medication (7%), obstetric complication (7%), or a neoplastic process (5%) can often be identified.

A concomitant autoimmune disorder such as systemic lupus erythematosus (40%), lupus-like syndrome (5%), or another autoimmune disease (9%) is frequently present.

Organ Involvement in CAPS

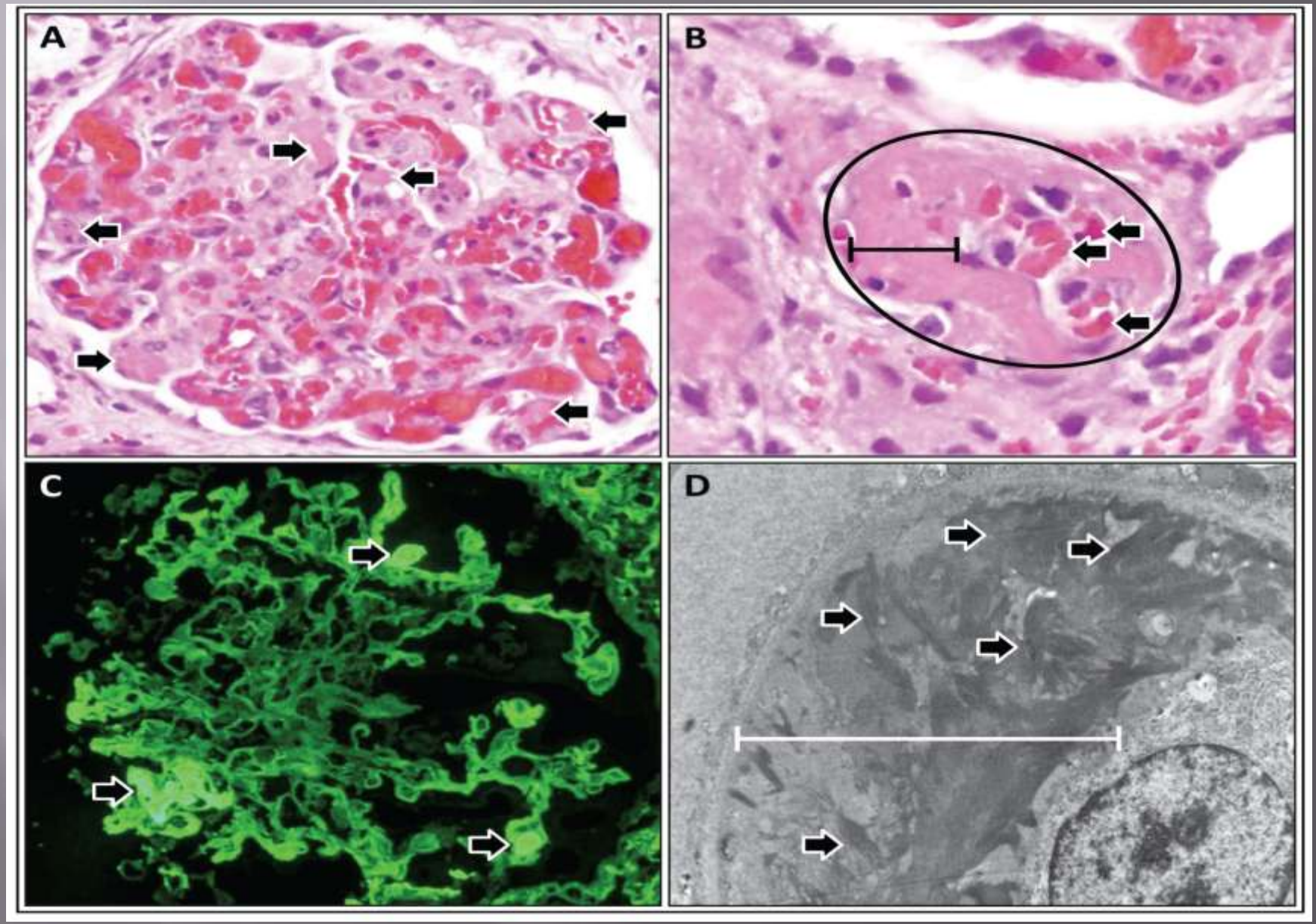
Kidney	71%
Lung	64%
Central Nervous System	62%
Heart	51%
Skin	50%
Liver	33%
Gastrointestinal tract	25%
Venous thrombosis	23%
Spleen	19%
Adrenal glands	13%
Arterial thrombosis	11%
Pancreas	8%
Retina	7%
Peripheral Nervous System	5%
Bone marrow	4%

Although renal disease is the presenting feature in only 18% of patients, kidneys are eventually involved in 71% of patients during the course of the disease.

Renal involvement is defined by a ≥50% rise in serum creatinine concentration, proteinuria (>0.5 g/day), severe hypertension (blood pressure >180/100 mm Hg), or a combination thereof .

The most frequent renal manifestations are hypertension, proteinuria, hematuria, and acute renal failure . Proteinuria ranged between 0.6 g/day and 6.1 g/day with a mean of 2.8 g/ day .

Hypertension is often severe. Renal infarction develops on a rare occasion


A
B
C
D

Laboratory Findings in CAPS

Anticardiolipin IgG 83%

Lupus anticoagulant 82%

Antinuclear antibodies 66%

Thrombocytopenia 46%

Anticardiolipin IgM 38%

Hemolytic anemia 35%

Schistocytes on blood film 16%

Acute-phase proteins ?

Treatment

A life-threatening systemic disease, CAPS requires an aggressive multidisciplinary collaborative treatment strategy.

The following treatments, often in combination, have been used for CAPS:

anticoagulation, glucocorticoids, plasma exchange, cyclophosphamide , intravenous immunoglobulins , and anti-platelet agents .

Off-label treatments, including rituximab, defibrotide, and eculizumab, have all been reportedly used for CAPS and have been proven to be beneficial.


Thank you